European Patent Office
D-80298 München
Germany

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BY FACSIMILE
Confirmation by Mail

Dear Sirs

International Patent Application No. PCT/GB03/02928 of National Blood Authority et al.

I write in reply to the Written Opinion dated 12 March 2004.

Amended page 36 of the claims is enclosed to replace page 36 as filed. The dependency of claim 14 has been corrected as suggested in Section III, paragraph 3 of the Written Opinion. The matters referred to in Section III, paragraphs 1 and 2 and Section V, paragraphs 5 and 6 of the Written Opinion will be addressed during the national/regional phases of this application.

The Written Opinion raised lack of novelty objections against claims 1, 3, 8 and 9 on the basis of D1, D2 and D5. It is submitted that none of these documents in fact deprive any of these claims of novelty, as none of them contain a clear and unambiguous disclosure of the subject matter of any of these claims.

D1 (JP-A-02193913) discloses use of a metal chelate chromatography medium to separate pyrogen from *inter alia* fibrinogen. Pyrogens are lipopolysaccharides derived from bacterial cell walls. They are not therefore proteins. D1 therefore only describes separation of a single protein (e.g. fibrinogen) from a non-protein substance (pyrogen). It does not describe any purification of fibrinogen from a starting material which contains more than one protein, as required by present claim 1. Furthermore, it does not refer to either plasminogen or factor XIII. There is therefore no disclosure of the separation of fibrinogen from plasminogen or the co-purification of fibrinogen and factor XIII as required by claims 3 and 7 respectively. Claims 8 and 9 are also novel, as D1 does not make any reference to plasminogen.

D2 simply discloses that Prosep Chelating III (an immobilised metal affinity chromatography product) "is suitable for the purification of large molecules such as fibrinogen". However, there is no disclosure or suggestion in D2 as to use of such a product for the separation of fibrinogen from another protein such as plasminogen. Nor is there any disclosure of the use of such products for the co-purification of fibrinogen and factor XIII. Claims 1, 3, 7, 8 and 9 of the present application are therefore novel over D2.

D5 is an equivalent of US5,169,936 which is referred to on page 3, lines 5-10 of the present application. D5 simply suggests that immobilised metal affinity chromatography (IMAC) could be used for the purification of human fibrinogen. However, fibrinogen is just one of a long list of potential proteins given in D5 and there are no examples of the use of IMAC for the purification of fibrinogen. Still less is there any disclosure of the use of IMAC for the separation of fibrinogen from other proteins including plasminogen, or for the co-purification of fibrinogen and factor XIII. D5 is not therefore relevant to novelty or inventive step of the presently claimed methods.

Insofar as Section V, paragraph 3 of the Written Opinion is concerned, D2 does not make any mention of factor XIII as a potential target protein for purification by metal chelate chromatography. In particular, there is nothing in D2 to lead a skilled person to use metal chelate chromatography for the simultaneous purification of fibrinogen and factor XIII. Therefore, claims 7 and 10 do not lack an inventive step over D2. Similarly, there is no suggestion in D2 that such chromatography could be used to separate fibrinogen from plasminogen. Claims 1, 3, 8 and 9 are also inventive.

As D1 contains no suggestion that fibrinogen could be purified from a solution containing at least one other protein using metal chelate chromatography, D1 is not relevant to the inventive step of claim 1. Similarly, there is no suggestion anywhere in D1 that metal chelate chromatography could be used to separate fibrinogen from plasminogen or to co-purify fibrinogen and factor XIII. Claims 3 and 7 are also therefore inventive over D1.

It is also pointed out that none of D1, D2 or D5 suggest that IMAC could be used for the preparation of both plasminogen and fibrinogen (as claimed in present claim 4) or the co-purification of fibrinogen and factor XII from a solution also containing plasminogen (as claimed in present claim 6). Therefore, these claims are also inventive.

In the light of the above arguments, it is hoped that the Examiner can now issue an International Preliminary Examination Report indicating both novelty and inventive step for at least claims 1-10 of the present application.

Please acknowledge receipt of this letter and enclosures by returning the EPO Form 1037 which accompanies the confirmation copy.

Yours faithfully
Frank B. Dehn & Co.

Annabel R. Beacham

Encl

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7. A method for the co-purification of fibrinogen and factor XIII which comprises the steps of:

(a) loading a solution comprising fibrinogen and factor XIII onto an immobilised metal ion affinity chromatography matrix under conditions such that the fibrinogen and the factor XIII both bind to the matrix, and

(b) selectively co-eluting the fibrinogen and the factor XIII from the matrix.

8. Use of immobilised metal ion affinity chromatography for the separation of fibrinogen from plasminogen.

9. Use of immobilised metal ion affinity chromatography for the preparation of fibrinogen and plasminogen.

10. Use of immobilised metal ion affinity chromatography for the co-purification of fibrinogen and factor XIII.

11. Fibrinogen prepared by a method according to any of claims 1 to 7.

12. Fibrinogen prepared by a method according to any of claims 1 to 7, for use in therapy.

13. A pharmaceutical kit comprising fibrinogen prepared by a method according to any of claims 1 to 7, together with thrombin.

14. A kit as claimed in claim 13, wherein the thrombin is prepared by a method comprising the steps of:

(a) solvent-detergent virus inactivation of a solution comprising prothrombin and factor X;

(b) loading the product of step (a) onto an anion